CONSIDERATIONS FOR RELIANCE ON SINGLE INSTITUTIONAL REVIEW BOARDS

by
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A capstone project submitted to Johns Hopkins University in conformity with the requirements for the degree of Master of Science in Research Administration

Baltimore, Maryland
December 2017

Abstract

The Collaborative Pediatric Critical Care Research Network has trialed several versions of the NIH mandated single IRB model in hopes to find the most efficient model. Study startup milestones were measured over four trials comparing the proficiency of the different versions. The biggest source of delay surrounds the complexity of an institution ceding implementation and review to another institution. Time and communication with key individuals is required to acclimate institutions to reliance on another institution.

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Glossary

HRPP	Human Research Protection Program
IRB	Institutional Review Board
CIRB	Central Institutional Review Board
CPCCRN	Collaborative Pediatric Critical Care Research Network
DCC	Data Coordination Center
NCATS	National Center for Advancing Translational Science
TIC	Trial Innovation Center
TIN	Trial Innovation Network
NIH	National Institutes of Health
NICHD	National Institute of Childhood and Human Development
AAHRPP	Association for the Accreditation of Human Research Protection Programs
VA	Veterans Affairs (Healthcare system)
PCH	Primary Children's Hospital
ERICA	Electronic Research Integrity and Compliance Administration
GIFT	GM-CSF for Immunomodulation Following Trauma
PICqCPR	Pediatric Intensive Care quality of CPR
iNO	Inhaled Nitric Oxide
PHENOMS	Biomarker Phenotyping of Pediatric Sepsis and Multiple Organ Failure
CHLA	Children's Hospital of Los Angeles
CHOM	Children's Hospital of Michigan
CHOP	Children's Hospital of Philadelphia
CNMC	Children's National Medical Center
DECH	Colorado Children's Hospital
MICH	University of Michigan
NWCH	Nationwide Children's Hospital
PHNX	Phoenix Children's Hospital

UCLA	University of California, Los Angeles
UCSF	University of California, San Francisco
UPMC	University of Pittsburgh Medical Center

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Considerations for Academic Medical Centers Relying on a Central Institutional Review Board

Chapter 1: Introduction

Improving clinical trial efficiency has been a common goal among research organizations, and much attention has been specifically focused on multi-center clinical trial start-up periods. There are several phases included in a clinical trial start-up period, including the protocol design and scientific peer review; the process to apply for and secure funding and resources; review by institutional Human Research Protection Programs (HRPPs), including Institutional Review Board (IRB) review, Conflict of Interest review, and other ancillary reviews; database creation; and recruitment of participants to secure enrollment. The use of single or Central IRBs (CIRB) has been posited as one method for increasing efficiency; however, when using a CIRB, it is important to consider how the other phases of the clinical trial start-up period are affected and can be optimized.

Centralization of the IRB process requires resources for managing submission to the CIRB and meeting the remaining local HRPP review requirements at each participating site. This may be accommodated through centralization of an administrative group between the CIRB and the participating sites, often titled a CIRB Liaison. This centralized administrative group may also be well

positioned to assist throughout the clinical trial start-up period, facilitating a smooth transition through each

phase. Centralization of such an administrative group requires a standardized procedure and workflow to ensure that efficient timelines for protocol development, CIRB submission and approval, and initiation of enrollment are maintained.

In 2012 the Collaborative Pediatric Critical Care Research Network (CPCCRN) and the University of Utah partnered to develop a CIRB process, a centralized administrative group, and a standardized procedure and workflow for clinical trial start-up for all research performed by CPCCRN. The CPCCRN Data Coordinating Center (DCC) assumed responsibility for this new procedure and workflow and became the centralized administrative group. More recently, the University of Utah was awarded by the National Center to Advance Translational Science (NCATS) to be a Trial Innovation Center (TIC) for the Trial Innovation network (TIN). One of the services that these TICs are offering is single IRB support for multi-institutional research projects and networks. A new partnership with this group was formed to further standardize and enhance the efficiency of this CIRB procedure.

Chapter 2: Background

In the past few decades, multicenter trials have become the new norm as opposed to single-center studies of the past, mainly due to

the scientific rigor or external validity required to support widespread changes in practice.[1] The Nation[1]al Institutes of Health (NIH) supports a variety of research networks fostering investigator-initiated multicenter clinical trials. As of June 21, 2016, the NIH released their final policy on the Use of a CIRB for Multi-Site Research. Newly funded PI's of multi-center studies are now expected to rely on a single IRB. This CIRB model is charged to carry out the functions that are required for institutional compliance with IRB review set forth in HHS regulations at 45 CFR 46.[2] A DCC that has expertise in handling all CIRB functions is critical since many investigators have very little experience working with and submitting their research to a CIRB (NIH, 2016). Little guidance is available in the peer-reviewed literature on the use of CIRBs for multicenter trials.[3] This capstone project will objectively outline the challenges and obstacles multi-institutional sponsored projects or research networks encounter when adhering to National Institute of Health (NIH) policy on central IRB. The goal of the project is to identify clearly, what issues are faced when making

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[1] Bellomo, R., 2009. *Why We Should be Wary of Single-Center Trials.* Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/19789447

[2] NIH, June 21, 2016. *Final NIH Policy on the Use of a Single Institutional Review Board for Multi-Site Research.* Retrieved from: https://grants.nih.gov/grants/guide/notice-files/NOT-OD-16-094.html

[3] Check, D. K., 2013. *Use of central institutional review boards for multicenter clinical trials in the United States: a review of the literature.* Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/23666951

the transition from local IRB review to CIRB review. A final goal of the project is to ascertain what processes were most effective in easing the burden of this transition and how they can help others planning on this transition in the future. The University of Utah IRB and Utah DCC have collaborated to create a CIRB of record for the CPCCRN.

Established in 2005, the CPCCRN consists of a team of eight academic clinical sites and a data coordinating center, as well as the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD). This network seeks to reduce morbidity and mortality in pediatric critical illness and injury and to establish a framework for developing the scientific basis for pediatric critical care practice. These goals cannot be achieved without the support of collaborative clinical trials otherwise impracticable in single institutions.[4] Research concepts are proposed and vetted through the network Steering Committee for approval, development, and implementation. When a final protocol has been scheduled for implementation, it is the responsibility of the DCC to make any agreed upon modifications and to distribute the protocol to network members. The DCC is then responsible for preparing the CIRB submission on

[4] Wilson, D. F., 2006. *Collaborative Pediatric Critical Care Research Network (CPCCRN).* Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/?term=willson+2006+collaborative+clinical+trials

behalf of the network. DCC project managers are experienced in preparing IRB applications and handling all aspects of IRB regulatory work on behalf of the investigator.

Prior to instituting the CIRB, the CPCCRN had done well during its first ten years in obtaining IRB approvals expeditiously. A rotating IRB model was used from the beginning of the network. The lead site would submit first to their IRB, making any adjustments required by their local IRB. Once the lead site had obtained approval, all sites would submit to their respective IRB's using the lead sites approved IRB application as a template. Use of a CIRB in the network began as an experiment to proactively comply with what the network expected to be a requirement in the near future from NIH and the proposed changes to the Common Rule. In addition, this decision was based on the fact that several network RFAs required network sites to use a central IRB. In addition, several federally sponsored meetings to "discuss" IRB models appeared to be meetings preparatory to requiring CIRB implementation. Initially, seven of the eight network sites had agreed to voluntarily rely on the Utah CIRB. One CPCCRN site declined participation, waiting until the requirement to use a CIRB became mandatory. The University of Utah CIRB experiment that began in 2013 has introduced different challenges, which will be addressed in this paper. Furthermore, the transition of the CIRB

liaison from the DCC to the Utah TIC has affected the challenges with new standardized procedures.

The DCC is a research facility located at the University of Utah that serves as the central biostatistical and logistical resource for the work of the CPCCRN. The DCC has experience with the coordination of multicenter clinical trials, and expertise in study design, clinical data management, IT solutions, and biostatistical analysis. In short, the DCC scope of activities includes assuring the successful execution of all scientific and administrative activities carried out by the Network, in collaboration with the NICHD, Steering Committee and Advisory Board. With the Utah TIC managing the CIRB process the DCC will supervise their effort to support the CPCCRN.

The University of Utah Human Research Protection Program is a complex biomedical and social behavioral enterprise with more than 5,000 active studies. The HRPP has maintained full accreditation from the Association for the Accreditation of Human Research Protection Programs (AAHRPP) since 2007. The IRB is comprised of seven review panels with over 100 members that meet up to three times per week in order to conduct thorough and timely reviews. The University acts as the IRB of record for the Veterans Affairs Salt Lake City Health Care System (VA) and Primary Children's Hospital (PCH), as well as many other affiliated hospitals, universities, government agencies, and

community partners. The HRPP has been managed by an automated, web-based system since 2006. The Electronic Research Integrity and Compliance Administration (ERICA) System allows HRPP members, including study teams, 24-hour access from any location with an internet connection to manage existing projects, submit new projects, and complete a wide variety of other tasks.

Chapter 3: Methodology

Challenges and obstacles for creating a multi-institutional compliance with NIH policy on central IRB

Implementing the CIRB process for CPCCRN was done in incremental steps. In spring 2012, the DCC PI posed the idea of creating a CIRB for the Network in conjunction with the proposed changes to the Common Rule. At that time, the Network consisted of seven Clinical Centers and eight sites. Each Clinical Center PI was tasked with opening a dialogue with their respective IRBs.

A reliance agreement is a written document that allows an institution to delegate the responsibilities of an IRB to a central IRB for the purpose of central management of multi-center studies (See Appendix A). These agreements are negotiated on a site-by-site basis between each participating site and the DCC and are the first step in

the CIRB process. Once a reliance agreement is in place, the site may rely upon that particular CIRB for any study between the institution and the same CIRB. During the initiation of the CIRB for CPCCRN, the process of getting these Reliance agreements in place took nearly a year. As the familiarity with Reliance Agreements has become more common, the timeline to obtain these agreements has generally decreased.

In late summer of 2012, negotiations for IRB reliance agreements began. Phoenix Children's Hospital signed the first agreement in November 2012. Other sites quickly followed. By May 2013, six sites had Reliance Agreements. An additional site's Reliance Agreement was executed in November 2013. In December of 2014, CPCCRN's grant cycle renewed; four sites were dismissed and four sites joined. Reliance Agreements for the four new sites were executed by February of 2015.

Following the decision to allow the Utah TIC to support CIRB functions for the network. The NCATS and TICs implemented a standard reliance agreement known as The SMART IRB Reliance Agreement (See Appendix B).[5] This standardized agreement

[5] SMART, 2017. *SMART IRB Homepage.* Retrieved from: https://smartirb.org/

streamlines the need to negotiate on a site-by-site basis since it requires all sites to follow the same procedures and policies operating multi-site research under NIH guidance. Throughout the period of this capstone, seven of the eight sites have signed this agreement. With only one site that is owned by a private entity not signing to date.

After all participating sites have executed reliance agreements and the DCC's IRB becomes the CIRB, the data coordination center submits a study application to the DCC's IRB on behalf of all the sites. The study application includes information about each of the participating sites and may include site-specific documents and consent forms. Once a study has CIRB approval, the study is effectively approved at all sites. Within CPCCRN, this application process has become more efficient thanks to the development of a standard Working Guideline. This working guideline contains consistent language and responses to questions asked in the CIRB application. These efficiencies benefit both the DCC staff submitting the application and the CIRB staff reviewing the application, resulting in shorter review times and faster CIRB study approvals.

<u>Issues institutions face when making the transition from a local IRB review process to a Centralized IRB review process</u>

Due to differences in state law and institutional practices, a good portion of consent language must be site-specific. Originally, in the CIRB process, sites completed their own consent documents, often requiring DCC staff to edit the same document and return it back to the site again for approval. This process resulted in multiple steps to arrive at a final draft. As a first attempt to minimize this effort, DCC staff locked certain sections of the consent forms, leaving other sections available for sites to edit for local requirements. However, this presented new issues with formatting and resulted in more back-and-forth. Finally, the current process with pre-approved, site-specific informed consent templates was developed which minimized the roadblock of the back-and-forth communication between the site and the CIRB. The template for each site contains the site's IRB-required standard language and is pre-approved by the site's IRB prior to the study application. When a new study is developed, the DCC adds study-specific information to the site-specific consent templates and submits the documents to the CIRB along with the study application. Utilizing these templates has improved timelines for the CIRB process.

Local review is a term used to describe site-level IRB approval of a CIRB submission. Local reviews occur after a reliance agreement has been executed and are not intended to be a full IRB review, as that responsibility has been delegated to a central IRB. The goal of

the local review is to ensure that any local requirements, such as conflict of interest or any ancillary reviews related to the study are met by the CIRB submission. Once the CIRB application is approved and a local review is completed by the site, the study is approved for enrollment at the site.

Finally, an additional innovation added the process by the NCATS TIC initiative included adding an online platform that allows the relying sites and the IRB of record or reviewing IRB to exchange information and communicate. Here, actions are documented and standardized for all sites using the SMART IRB reliance agreement. This allows IRBs to identify who is the IRB of record and who the relying sites are. Relying sites can cede review for every project they are invited to participate in, relying sites can provide a profile of their institution, and local requirements that the IRB of record needs to know. The exchange provides a location for documentation that local review has been completed and interchange submission approvals and documents such as informed consents or surveys across the network or multi-institutional trial.[6]

[6] SMART IRB Exchange, 2017. *SMART IRB Exchange – About Us.* Retrieved from: https://trialinnovationnetwork.org/smart-irb-exchange/

Chapter 4: Anticipated Results and Outcomes

The effectiveness of processes used to achieve the transition

Early in the CIRB process, the DCC prepared would prepare an Informed Consent document for the study as a template, including all science and procedural information. This Informed Consent template was then sent to the site to include the site's locally required language. This process necessitated a lot of back and forth with the site, culminating in weeks of delay. It was discovered that some of the sites' IRBs had specific preferences that contradicted the CIRB's requirements, such as the required footer or header information. This led to the development of site-approved consent templates, which included all locally required information. The DCC uses these templates to insert the science and procedural information and the consent is ready for submission.

Another challenge encountered by the DCC was in how the applications (original, amendment, continuing review) were being assigned and reviewed by the Utah IRB staff. IRB reviewer assignments are made by the day the application is submitted. This resulted in many different IRB staff reviewing the DCC's CIRB submissions. Due to this, the DCC struggled with varying requests for revision, sometimes from the reviewer's lack of experience working the

CIRB submissions. Once this challenge was identified, the DCC had a face-to-face meeting with all key players between the DCC and IRB staff. This resulted in creating an open dialogue between our institutions and provided clarity on some of the issues at hand.

Since the network already had an efficient IRB submission process, the DCC collected time and effort data on the new method of submitting to a CIRB. It is important to evaluate which submission method is more efficient for the network, the rotating model of submitting the lead site first with all other sites following or submission to a single IRB. DCC Project Managers were assigned to collect various data points to answer this question. This data was collected for three years. Data was collected the following data on each study involving the CIRB: the date each site was approved to submit to their local IRB, the date each site actually submitted to their local IRB, the date each site received IRB approval, number of days from time to submission to approval, the date each site was approved to begin enrolling and the date of each site's first enrollment. These data were collected for the original IRB/CIRB submission. Similar data were tracked for amendments and continuing reviews, which are not discussed in this project. Performance metrics for the first five CIRB studies are presented in Table 1. These data highlight that the Utah CIRB is very efficient, with a mean time of 28.6 calendar days between

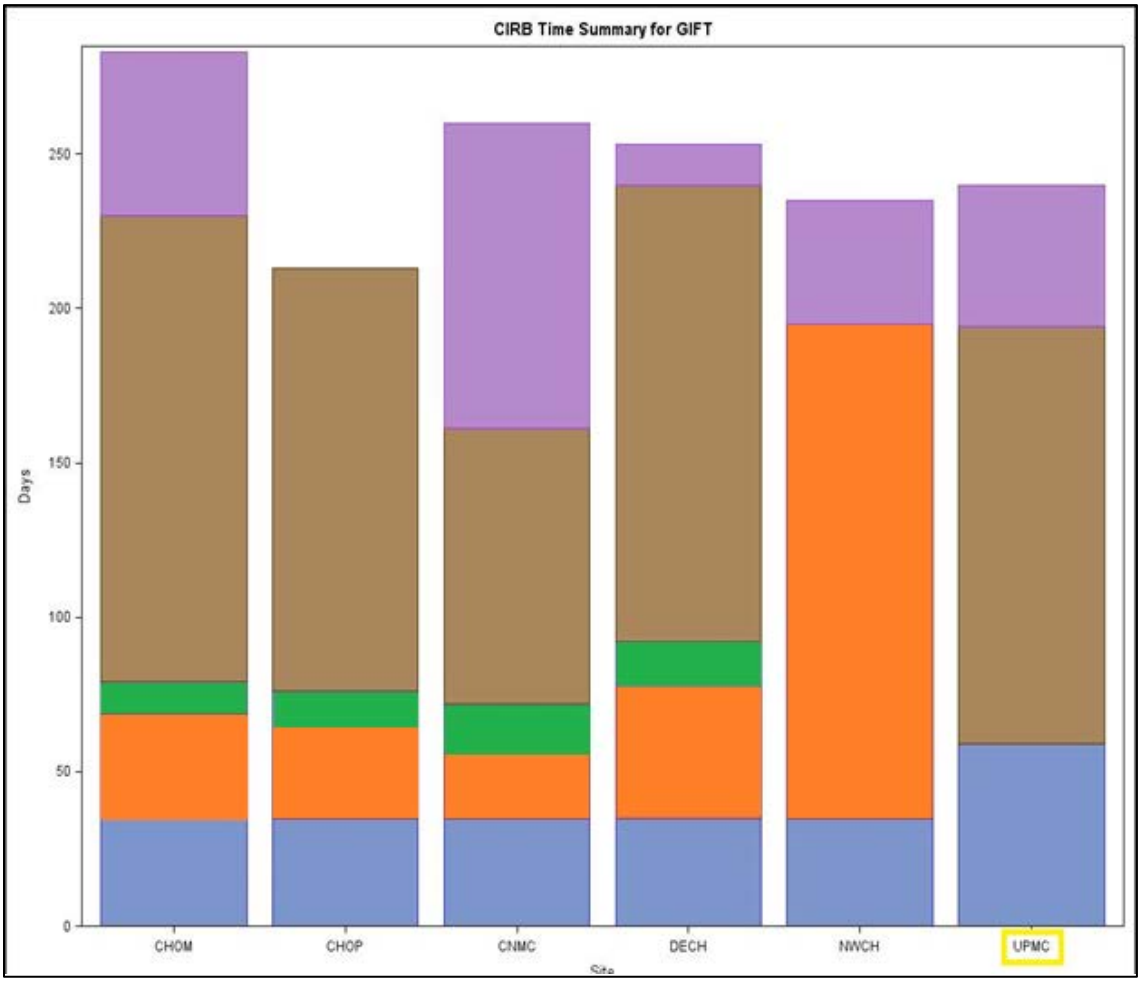
protocol submission and CIRB approval. Overall, five protocols were reviewed on behalf of twenty-eight sites. Following CIRB approval, on average it took 80.6 days to complete local HRPP before screening could begin. This was recognized as an area needing improvement. The reason for this delay is primarily to do with local IRBs performing redundant IRB reviews in addition to HRPP local reviews. With time, relying IRBs will need to accept the CIRB review and not perform the task twice.

Table 1: Central IRB performance metrics (all times are in calendar days)

Name of Trial	Number of cIRB sites	Protocol submission to cIRB approval	cIRB approval to local IRB approval at 50% of cIRB sites	cIRB approval to local IRB approval at 90% of cIRB sites	cIRB approval to first enrollment	cIRB approval to first enrollment at 50% of cIRB sites	cIRB approval to first enrollment at 90% of cIRB sites
BATE	3	23	48	83	56	59	91
PEACE	5	24	32	78	108	108	248
PICqCPR	6	37	35	43	36	53	69
PHENOMS	7	28	39	144	59	108	178
LAPSE	7	31	35	55	29	77	175
	Mean:	28.6	37.8	80.6	57.6	81	152.2

Below are tables that further break down the time spent on specific network project original submissions. Data for tables 2 - 5 were collected from historical and real time milestones for sites participating in the specified CPCCRN projects. The data was documented and retrieved from IRB approval documents at the CIRB and local IRBs. The discussion of table data and site nuances includes details provided from the project managers assigned to those projects. Each table allows for some comparison between local submissions versus CIRB submission due to site variances of reliance on the CIRB at the time of project startup. Explanations for each project are provided below each table.

Table 2: GIFT Study Startup Timeline by Site

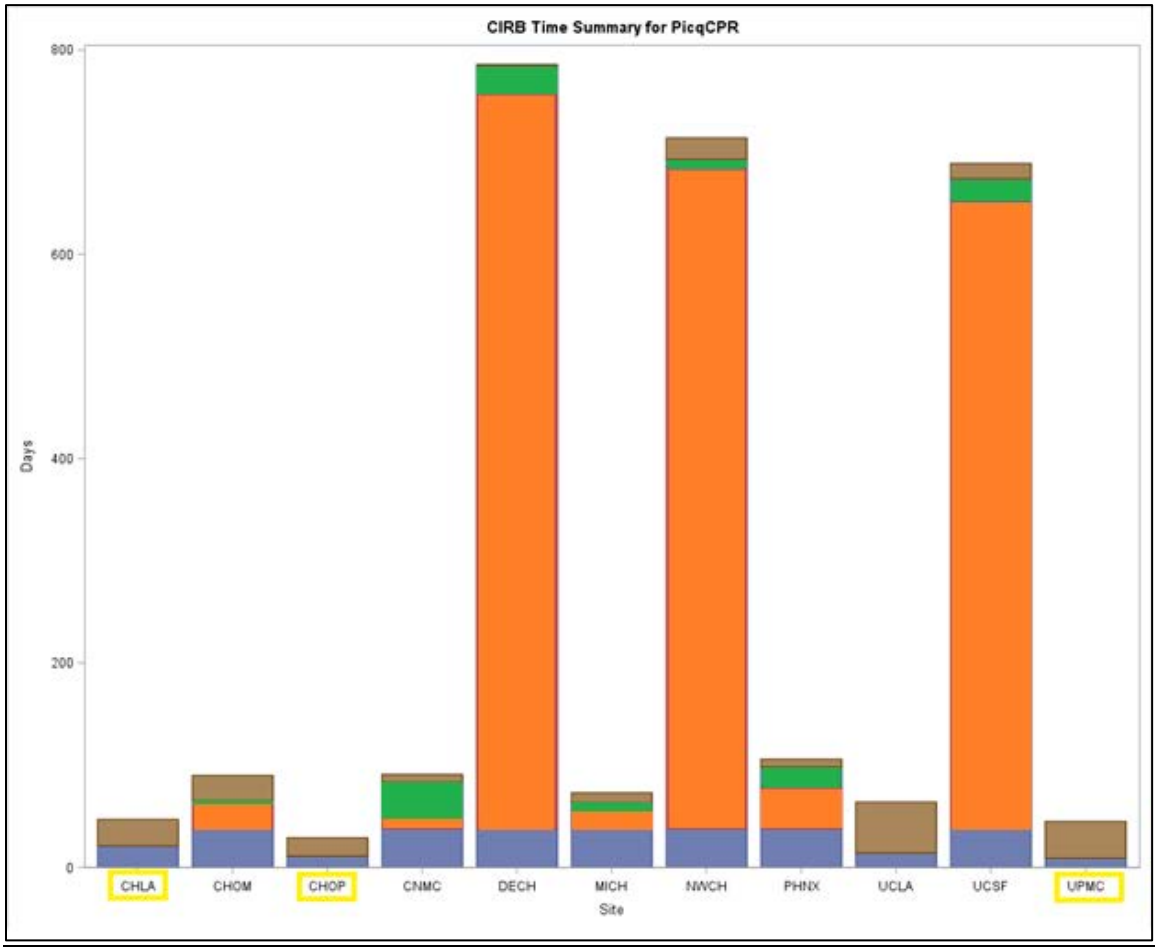


Blue: Days from original submission to IRB/CIRB approval. Orange/Green: Days from CIRB approval to local review approval (local review submission date is denoted by the line between orange/green). Brown/Purple: Days from local review approval to first enrolled subject. Contract execution date is denoted by the line between brown/purple. Yellow highlighted sites do not participate in the CIRB.

GIFT was originally a single-center trial at Nationwide Children's Hospital. In 2014, the PI of GIFT was accepted into CPCCRN and subsequently granted permission to expand the trial to the other

CPCCRN sites. The CIRB for this study included all CPCCRN sites, except for one. The lead site, Nationwide Children's Hospital opted to remain on their local IRB until formal NIGMS (funding agency) approval was granted. Their local review application was submitted and approved the same day. Due to the nature of the research, GIFT is a slow enrolling study. Despite this, some sites took longer to begin enrolling subjects because contracts were not fully executed.

Table 3: PICqCPR Study Startup Timeline by Site

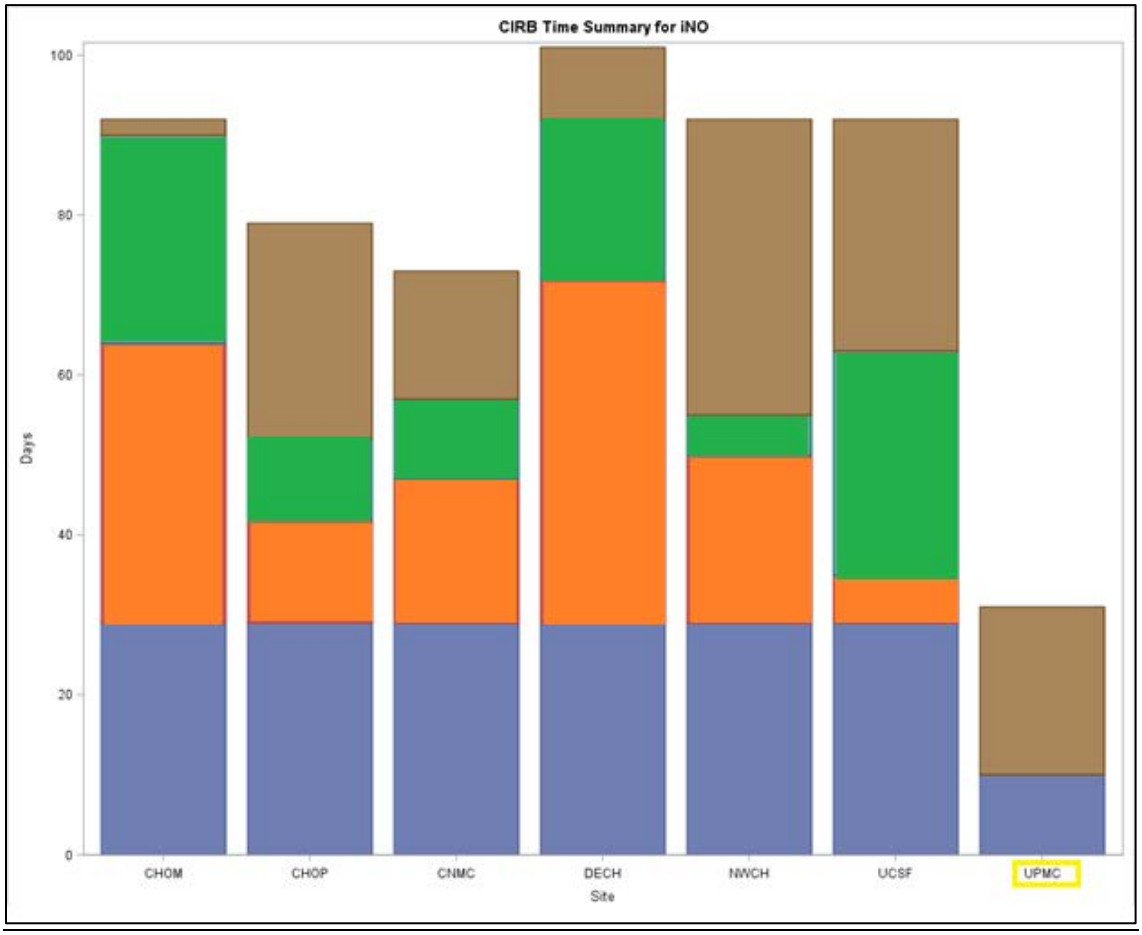


Blue: Days from original submission to IRB/CIRB approval. Orange/Green: Days from CIRB approval to local review approval (local review submission date is denoted by the line between orange/green). Brown/Purple: Days from local review approval to first enrolled subject. Contract execution date is denoted by the line between brown/purple. Yellow highlighted sites do not participate in the CIRB.

PICqCPR is a good project to demonstrate the difference between local and central review with roughly half the sites using local IRB review and the other half using the CIRB model. CIRB sites have the same

time for IRB review followed by a site-specific period of local review. Once a site has local review approval they are allowed to screen and enroll. Local IRB sites, highlighted in yellow, have a local review period followed directly by screening and enrolling and do not have a local review period. It should be noted that the sites dominated by the color red were introduced to the study approximately two years after enrollment had begun for other sites. The local review period for these sites began when approval to submit their local review was given rather than the CIRB approval that occurred two years prior. These three sites took the longest to obtain local review approval due to PICqCPR being their first exposure to the CIRB model and time was needed to initiate reliance agreements. Additionally, the DECH site was delayed in obtaining local review approval due to delays in executing the subcontract.

Table 4: iNO Study Startup Timeline by Site

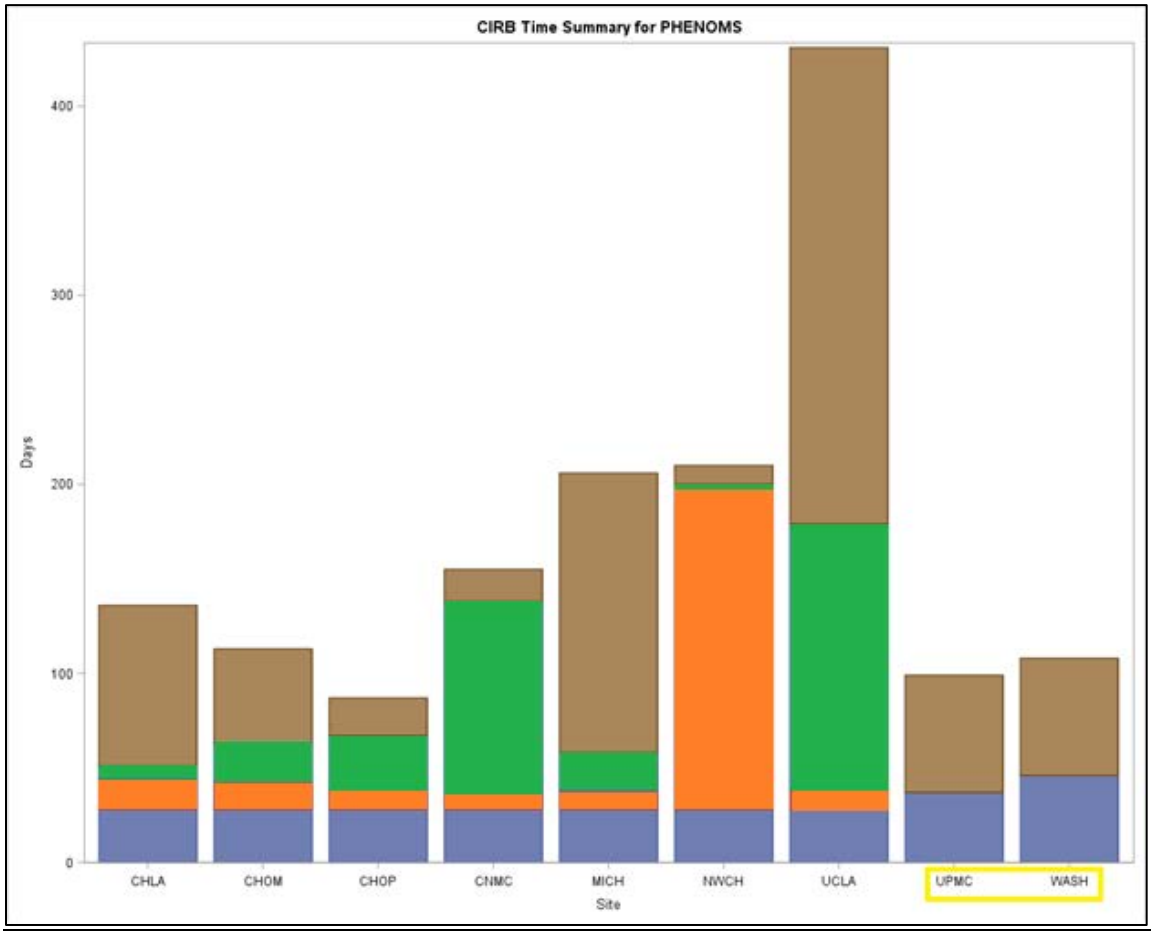


Blue: Days from original submission to IRB/CIRB approval. Orange/Green: Days from CIRB approval to local review approval (local review submission date is denoted by the line between orange/green). Brown/Purple: Days from local review approval to first enrolled subject. Contract execution date is denoted by the line between brown/purple. Yellow highlighted sites do not participate in the CIRB.

All but one of the sites participating in the iNO study relied upon the CIRB. The site not participating in the CIRB (UPMC) submitted an application to their own IRB for full review and was able to receive approval within 10 days of submission, substantially faster than the

CIRB approval. Two CIRB sites (CHOM and DECH) had much longer local review approval times when compared to the other sites. Delays at these sites were due to extra local administrative approval processes, which are in addition to local IRB reviews. While these two sites had delays in approval, their time to first enrollment was shorter than the other sites. As these sites waited for approval, they were able to train and prepare for the launch of the study. Once approval was granted, they were able to enroll quickly.

Table 5: PHENOMS Study Startup by Site



Blue: Days from original submission to IRB/CIRB approval. Orange/Green: Days from CIRB approval to local review approval (local review submission date is denoted by the line between orange/green). Brown/Purple: Days from local review approval to first enrolled subject. Contract execution date is denoted by the line between brown/purple. Yellow highlighted sites do not participate in the CIRB.

There are currently nine clinical centers participating in PHENOMS, seven of which participate in the Utah CIRB. On September 23, 2014, all CIRB participating sites were approved to submit the CIRB approved protocol to their local IRB for local review acknowledgment

and/or approval. Based on the CIRB Paper Time Summary for PHENOMS Table, three sites (CHLA, CHOM, and CHOP) received study approval and enrolled their first subject within or less than 150 days. The IRBs at two sites (CNMC and NWCH) required a full submission even though the sites participate in and cede to the Utah CIRB. As a result, for these two sites, the time from local review approval to the first subject enrolled was greater than 100 days. Two other sites (MICH and UCLA) were not renewed as network sites. In addition, both sites experienced staff turnover affecting time of the first subject enrolled. Lastly, as evident from the Table, the time of approval to the first subject enrolled for non-CIRB participating sites (UPMC and WASH) was relatively shorter than CIRB participating sites; less than 100 days.

Chapter 5: Analysis

Tables 1 - 5 and descriptions demonstrate that startup at multiple institutions is highly variable regardless of IRB model because of external factors not related to IRB review. In general, at study startup, there is no compelling evidence that CIRB is faster than local review. However, initial data collected for amendments and continuing reviews present persuasive evidence that the CIRB model is substantially faster than the local model. Although this data is not presented or included in this project at this time.

Lessons learned from the transition that can benefit other institutions

Lessons learned from this project focus around the goal of standardizing agreements and processes. Such as the SMART IRB and SMART IRB Exchange introduced by the NCATS TIC team. In principle, once the SMART IRB agreements and SMART IRB Exchange platform are operational and all sites are trained and feel comfortable, it is highly likely that the process will be expedited and improve the timelines demonstrated through the initial projects presented in this project.

Standardization across institutions in multi-center research will optimize speed and completion of the necessary tasks of startup. However, this project has identified several roadblocks to standardization. Almost every institution has resisted agreeing to the standard SMART IRB Reliance Agreement. The reasons for each site varies due to different policies and variances in legal counsel opinions from site to site. This was overcome by improving communication between the involved legal parties at the site and from the SMART IRB agreement developers at Harvard. CIRB liaison involvement or site PI and research team participation proved to be ineffective at expediting the signing of the agreement.

Based on site feedback, an additional roadblock to standardizing the process includes the SMART IRB Exchange platform meant to advance and improve review board communication and documentation transparency between network IRBs has proven to be even more challenging than the SMART IRB agreement. This is mainly due to the lack of formal training on the platform. Site IRBs and research teams never received any training or instruction from the NCATS TIC team. As a result, participation has been slow and uneven across all sites. This process is still underway in the CPCCRN despite efforts from NCATS TIC representatives and or DCC effort to educate sites. The best solution to date includes scheduling webinars with site research teams, site IRB representatives, CIRB representatives, NCATS TIC staff and DCC staff to train every one of the uses of the exchange and answer questions.

Final obstacles to this standardization process, specific to CPCCRN, include the already functional CIRB process put in place by the DCC team prior to the NCATS TIC changes implemented more recently. Because sites were used to the previous functional CIRB process, there has been major resistance to the NCATS changes that other networks and studies that did not have a CIRB process in place have seen. As a result, CPCCRN sites have felt no urgency to transition to these standard approaches introduced by the NCATS and

prefer to follow old processes. The saying “you cannot teach an old dog new tricks” strongly comes to play when making changes in a multi-institutional environment. In this case, the best solution is to bolster sponsor support. NICHD support has required sites to transition to the NCATS changes. Even with sponsor guidance, the process continues at this time and full transition has not occurred for the CPCCRN.

In conclusion, the study startup period is compounded by many steps that extend beyond IRB review. Whether the review is local or central, the work must be shifted from one site to another to manage the required task of study startup. When complying with requirements to utilize central review for multi-institutional research, communication and education must be provided early and consistently throughout the transition and even after. Phone calls and face-to-face meetings extend the value of communication substantially more than simple email. Moreover, when standardizing these processes for multiple sites and networks, great patience is needed due to variances from site to site. Formal training for these standard procedures is optimum and leadership support is crucial to creating motivation at each site to implement new procedures.

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Appendix A

Reliance Agreement Template

RELIANCE AGREEMENT

This agreement allows the University of Utah IRB (UIRB) to act as the IRB for an external institution or external investigator. The external institution or external investigator is not required to have a Federal-wide Assurance (FWA) in order to use this agreement.

DIRECTIONS FOR USE OF THIS TEMPLATE:

- *This agreement should be signed by the external institution's signatory official or by the external investigator, as applicable.*
- *If the study is FDA regulated, the UIRB's signatory official must also sign this agreement.*
- *If the external institution or investigator has a FWA, the UIRB's signatory official must also sign this agreement.*
- *Instructions and text red font should be replaced or deleted.*

I. Purpose

This Reliance Agreement sets forth the agreement between the University of Utah and <<insert name of external institution or investigator>> concerning the agreed upon arrangements between the same for the use of the University of Utah's Registered Institutional Review Board (UIRB).

- The University of Utah maintains Federal Wide Assurance Number FWA00003475 assigned by the Office for Human Research Protections (OHRP).
- <<Insert name of external institution>> maintains Federal Wide Assurance Number <<insert FWA number>> signed by OHRP. ***Delete this bullet if your institution does not maintain a FWA.***

This agreement concerns the reliance of <<insert name of external institution/investigator>> on the review and approval by the UIRB, as specified in this agreement. This agreement sets forth respective authorities, roles and responsibilities of each party in such arrangement.

Those signing below agree that <<insert name of external institution/investigator>> may accept and rely on the review and approval by the UIRB of research involving human subjects as specified in this agreement. <<Insert name of external institution/investigator>> will abide by all determinations of the UIRB and will accept the final authority and decisions of the UIRB including but not limited to directives to terminate participation in designated research activities.

II. Types of Research Covered by this Agreement

This agreement is limited to the following specific protocol(s):

IRB Number:	<<insert number>>
Title of Study:	<<insert title>>
Principal Investigator:	<<insert name>>
Sponsor or Funding Agency:	<<insert sponsor>>

OR

This agreement applies to human subject research that is <<describe they types of studies that will be covered in this agreement, e.g. studies regulated by the Food and Drug Administration (FDA), all studies conducted by the institution, all studies from a specific department, etc. >>. Only human subject research for which both UIRB and <<insert name of external institution/investigator>> have agreed that review will be ceded to the UIRB will be included in this agreement.

Insert the following after the description of the types of research covered by the agreement:
This agreement does not preclude <<insert name of external institution/investigator>> from taking part in research not covered by this agreement.

III. Compliance with Federal Agency Guidance

This agreement meets federal requirements for designation of another institution's IRB as the reviewing IRB, as set forth in guidance issued by the Office for Human Research Protections (OHRP) entitled, *Terms of the Federalwide Assurance* (current as of June 17, 2011).

IV. Compliance with Federal and State Law and University of Utah Policy

Review and approval of human subject research under this agreement shall be conducted in compliance with the federal regulations as codified in 45 CFR 46 and 21 CFR 50 & 56 (as applicable), other pertinent federal regulations, state and local laws, and all applicable University of Utah policies pertaining to the protection of human subjects participating in research.

V. Informed Consent

Research subject to this agreement must employ a consent process, including a consent form, except when a waiver of informed consent is approved by the UIRB according to 45 CFR part 46 and 21 CFR 50 regulations. The UIRB will make available the University of Utah

Consent Template for use for research specified in this agreement. Modifications will be expected as to customize the form for the external site. Modifications will be subject to approval by the UIRB. <<Insert name of external institution/investigator>>, when responsible for enrolling subjects, will obtain, document and maintain records of informed consent for each such subject or each subjects legally authorized representative as required under 45 CFR part 46 and 21 CFR 50 regulations, as applicable.

VI. HIPAA Form of Authorization

<<Insert name of external institution/investigator>> defers HIPAA Privacy Board Determinations to UIRB which may include a HIPAA authorization, a waiver of authorization, and/or use of a limited/de-identified data set. <<Insert name of external institution/investigator>> must abide by HIPAA determinations made by the UIRB and must submit any additional forms (e.g. Notice of Privacy Practices, Information for Accounting of Disclosures, etc.) as necessary.

<<Insert name of external institution/investigator>> may use its own form of HIPAA authorization instead of the authorization language included in the University of Utah Consent Template. In this case, <<insert name of external institution/investigator>> will ensure that its form of authorization explicitly permits PHI to be used and shared by and with the University of Utah as necessary for reviewing and overseeing the research as specified in this agreement. Both the University of Utah and <<insert name of external institution/investigator>> are responsible for ensuring that information is shared in a HIPAA-compliant manner.

VII. Duties and Responsibilities of UIRB

a. ***Review and Authority***

The UIRB will conduct initial and continuing reviews. The UIRB will approve consent forms for all sites. The UIRB will review amendments to approved protocols. The UIRB will review information which requires reporting (i.e. unanticipated problems involving risks to participants or others, non-compliance, protocol deviations, etc.) for all sites**.**

The UIRB has the authority to suspend or terminate approval of research that is not being conducted in accordance with the UIRB policies, is not in compliance with Federal Regulations or that has been associated with unexpected serious harm to participants.

VIII. Duties and Responsibilities of <<insert name of External Institution or Investigator>>

a. ***Human Subject Research Guidance***

<<Insert name of external institution/investigator>> has reviewed:

- *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research* (or other internationally recognized equivalent; see section B.1. of the Terms of the Federalwide Assurance (FWA) for International (Non-U.S.) Institutions);
- The U.S. Department of Health and Human Services (HHS) regulations for the protection of human subjects at 45 CFR part 46 (or other procedural standards; see section B.3. of the Terms of the FWA for International (Non-U.S.) Institutions);
- The FWA and applicable Terms of the FWA for the University of Utah; and
- The relevant University of Utah policies and procedures for the protection of human subjects.

The <<Insert name of external institution/investigator>> understands and accepts the responsibility to comply with the standards and requirements stipulated in the above documents and to protect the rights and welfare of human subjects involved in research conducted under this agreement. No subjects may be enrolled in research under this agreement prior to the research's review and approval by the UIRB.

b. ***Facilitated Review***

<<Insert name of external institution>> will conduct a facilitated review locally, according to their local policies. A facilitated review is the process by which <<insert name of external institution>> may accept and rely on the approval issued by the UIRB. ***Delete this section if a facilitated review is not conducted at the external institution or this agreement is with an individual external investigator.***

c. ***Investigator Responsibilities***

Investigators conducting research subject to this agreement are responsible for reviewing the PI Responsibilities and the PI Statement of Assurance (available on the UIRB website). Investigators must abide by the stipulations described in the Statement of Assurance. Investigators will agree to the Statement of Assurance when submitting a research protocol through the Electronic Research Integrity and Compliance Administration (ERICA) program.

The PI is responsible for submitting the new study application and any subsequent continuing review applications. The PI is responsible for submitting amendments, report forms and the final project report, as applicable.

d. ***Local oversight***

<<Insert name of external institution/investigator>> will maintain oversight for local unanticipated problems involving risks to participants or others and local non-compliance.

e. ***Authority to Audit***

<<Insert name of external institution>> retains authority to conduct audits to ensure compliance. ***Delete this section if this agreement is with an individual external investigator.***

f. ***Conflict of Interest***

<<Insert name of external institution>> is responsible for evaluating the potential financial conflicts of interest of its investigators and research staff, according to <<insert name of external institution>> policy. <<Insert name of external institution>> will report all financial conflicts to the UIRB. ***Delete this section if this agreement is with an individual external investigator.***

IX. Duties and Responsibilities of both the UIRB and <<insert name of External Institution or External Investigator>>

a. ***Federalwide Assurance***
Both the University of Utah and <<Insert name of external institution>> have FWAs and so agree to abide by all applicable regulations in the conduct of human subjects research at each facility. ***Delete this paragraph if the external institution does not have an FWA or this agreement is with an individual external investigator.***

b. ***Agreement on File***
Both the UIRB and <<insert name of external institution/investigator>> agree to keep this Reliance Agreement on file at the respective institution and made available upon request to OHRP or any U.S. federal department or agency conducting or supporting research to which the FWA applies.

c. ***Policies and Procedures***
Both the UIRB and <<insert name of external institution/investigator>> agree to develop or maintain standard operating procedures consistent with this agreement.

d. ***Communication and Cooperation***
Both the UIRB and <<insert name of external institution/investigator>> agree to maintain effective communication and cooperation mechanisms sufficient to ensure adequate protections for human research subjects. Both institutions agree to fully cooperate with the reciprocal IRB including providing relevant documentation and records as needed.

e. ***Event Reporting***
Both the UIRB and <<insert name of external institution/investigator>> agree to promptly inform to the reciprocal institution of reports of serious or continuing noncompliance in the conduct of the study and unanticipated problems involving risks to participants or others, encountered in research as specified in this agreement.

X. Notices and Primary Contacts

a. Any notices to the undersigned institutional officials or correspondence regarding IRB review and oversight must be addressed as follows:

If to UIRB:
Thomas N. Parks, PhD Vice President for Research University of Utah 201 South Presidents Circle, Room 210 Salt Lake City, UT 84112 Phone: 801-581-7236 Email: tom.parks@utah.edu John Stillman IRB Director University of Utah 75 South 2000 East, #111 Salt Lake City, UT 84112

Phone: 801-587-9136 Fax: 801-587-9138 Email: john.stillman@hsc.utah.edu Ann Johnson IRB Associate Director University of Utah 75 South 2000 East, #111 Salt Lake City, UT 84112 Phone: 801-587-9134 Fax: 801-587-9138 Email: ann.johnson@hsc.utah.edu

If to <<insert name of applicable external institutional official(s)/investigator>>:
<<Insert name(s), title(s), address(es), phone number(s), fax number(s), and email address(es)>>

Signature of External Institution's Signatory Official:

_____ Signature	_____ Date
_____ Print Full Name	_____ Institutional Title
Address:	
Phone:	

Signature of Signatory Official (University of Utah):

_____ Signature	_____ Date
_____ Print Full Name	_____ Institutional Title
Address:	
Phone:	

Appendix B

SMART IRB Reliance Agreement

Master Common Reciprocal Institutional Review Board Authorization Agreement

Introduction

The purpose of this SMART IRB Master Common Reciprocal Institutional Review Board Authorization Agreement ("Agreement") is to support Institutional Review Board ("IRB") reliance in facilitation of multi-site human subjects research. The Agreement allows Participating Institutions (defined below) to cede IRB review ("Relying Institution") to the IRB ("Reviewing IRB") of another Participating Institution ("Reviewing IRB Institution").

Developed under an award from the National Center for Advancing Translational Sciences ("NCATS"), the National Institutes of Health (NIH), the Agreement sets forth the respective authorities, roles, and responsibilities of the parties when a Ceded Review (defined in Exhibit A) is determined to be acceptable by Participating Institutions in accordance with the process set forth herein.

This Agreement is open to participation by any institution that (i) meets the eligibility requirements outlined herein and (ii) agrees to accept the terms and conditions of the Agreement through the execution of a Joinder Agreement, as further set forth in Section 1 below ("Participating Institution").

This Agreement is also open to participation on the same conditions by any independent IRB organization that provides IRB review services ("IRB Organization"). The terms "Participating Institution" and "Reviewing IRB" as used herein, and all rights and obligations of Participating Institutions and Reviewing IRBs hereunder, shall include and apply to IRB Organizations unless otherwise noted herein.

A glossary of all acronyms and capitalized terms used in this Agreement, whether or not they are defined within the body of the Agreement, is provided at Exhibit A, which is attached hereto and incorporated by reference herein.

This Agreement meets federal requirements for designation of another Participating Institution's IRB as the Reviewing IRB. This Agreement shall be kept on file at each Participating Institution and shall be provided to the Office for Human Research Protections ("OHRP") or other federal agencies upon request.

1. Eligibility and Process To Participate in the Agreement

An Institution is eligible to participate in this Agreement if it meets the following requirements:

1.1 FWA; Oversight of All Research. Unless it is an IRB Organization, the institution must maintain an OHRP-approved Federalwide Assurance ("FWA"), regardless of whether it engages in federally funded human subjects research that is subject to the Federal Policy for the Protection of Human Subjects ("Federal Policy"). In addition, the institution, by policy or otherwise, must require IRB review and provide institutional oversight of its human subjects research regardless of funding source or the scope of its FWA. In the case of human subjects research that would be exempt from IRB review under Federal Policy, the institution must still provide institutional oversight of such research. Such policy need not require, and this Agreement does not require, reporting unanticipated problems, serious or continuing noncompliance, or suspension/termination of such research to OHRP or other agencies when such reporting is not required by the institution's FWA or policies or otherwise by regulation. However, nothing in the institution's policies may *preclude*, and this Agreement shall not preclude, the institution from reporting such events to OHRP or other agencies in such circumstances. The institution must inform all Participating

Biography

Richard Whitney Coleman, B.S.N., R.N., C.C.R.C., Mr. Coleman is the Program Director of the Collaborative Pediatric Critical Care Research Network (CPCCRN). Prior to this appointment, he was a Project Manager in the CPCCRN, managing large multicenter network projects. He graduated from Johns Hopkins University in the Masters of Research Administration (MRA) program December 2017. His Bachelor's degree comes from the University of Utah's Nursing Program in 2010. Other work experience includes Clinical Research Coordinator with NeuroNEXT and years as a Clinical Research Nurse for the CTSA at the University of Utah. Whit is a recognized leader in clinical research at the University of Utah and has extended his leadership influence outside the university, through his support of NeuroNEXT and the CPCCRN. He is an effective public speaker and speaks nationally as an expert in rare diseases. He is fluent in Spanish. His clinical skills include ACLS and PALS certification and is knowledgeable in dealing with a diverse group of disease states in the research setting due to his diverse background and extensive experience on over 200 protocols.

Mr. Coleman is responsible for day-to-day operations of the CPCCRN. Mr. Coleman interviews, hires, trains, mentors and supervises all Project Managers. He attends all Steering Committee meetings and

teleconferences, prepares regular reports for the NICHD, and negotiates contracts as needed with central laboratories, pharmacies, and site monitoring companies.